DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Christine Duffy Smith
Promotional Regulatory Affairs, Director
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

RE: IND # [redacted] ZD1839
[redacted] ZD0473
[redacted] ZD1694 (tomudex)
[redacted] ZD9238 (faslodex)
NDA# 20541 Arimidex (anastrozole) tablets
MACMIS ID# 10135

Dear Ms. Duffy Smith:

This letter notifies AstraZeneca Pharmaceuticals LP (AstraZeneca) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional activities that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, AstraZeneca is promoting Arimidex for an unapproved use and promoting its investigational new drugs, ZD1839, ZD0473, ZD1694 (tomudex), and ZD9238 (faslodex), as safe or effective. Our specific objections follow:

Promotion of Unapproved Uses

Arimidex is indicated for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer and for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. AstraZeneca distributed an abstract entitled *The Combined Use of Goserelin and Anastrozole as Second Line Endocrine Therapy in Premenopausal Women with Advanced Breast Cancer - a Study of its Clinical and Endocrine Effects* at their commercial exhibit at the 37th American Society of Clinical Oncology (ASCO) Annual Meeting held in San Francisco, California in May 2001. The abstract states "This study shows that Z [Zoladex (goserelin)] + A [Arimidex] induces therapeutic remission in a reasonable proportion of premenopausal women with advanced breast cancer who have progressed on Z+T [tamoxifen]. The clinical therapeutic effects are associated with demonstrable endocrine changes including a dramatic reduction of E2 levels seen in post-menopausal women receiving A alone."

The disseminated materials are violative and show that AstraZeneca intends for Arimidex to be used for an unapproved new use. Further, the small statement in the lower right corner of

the disseminated abstract ("For Medical Information Only–Not approved in the US") does not correct the violative promotion of an unapproved use for Arimidex in the commercial exhibit hall.

Promotion of Investigational Drugs

The AstraZeneca booth in the commercial exhibit hall of the May 2001, ASCO Annual Meeting includes convention panels describing the safety or effectiveness of ZD1839 and ZD1694 (tomudex), that are investigational drugs. Moreover, AstraZeneca disseminated promotional materials in two plastic containers, as well as copies of abstracts, that were available throughout the commercial exhibit area. One plastic container is labeled "ZD1839 ('Iressa') Medical Information Pack" and contained eighteen color copies of poster presentations and two slide kit handouts that made conclusions about the safety or efficacy of this investigational drug. The other container is labeled "A new generation platinum agent Medical Information Pack" and also contained numerous abstracts and color copies of poster presentations that made conclusions about the safety or efficacy of the investigational drug ZD0473. In addition, other loose abstracts, disseminated at the commercial booth, made conclusions about the safety or efficacy of the investigational drug ZD9238 (faslodex).

These convention panels and promotional materials include conclusionary statements such as:

ZD1839

"ZD1839 in combination with standard cytotoxics was well tolerated and showed enhanced tumor activity compared with treatment with either ZD1839 or cytotoxics alone."

"ZD1839 in combination with standard cytotoxics was associated with a significant increase in survival in vivo, particularly in combination with paclitaxel."

"Orally administered ZD1839 is active against central nervous system tumors with limited or no systemic toxicity."

"ZD1839 oral administration was well tolerated in patients with solid malignant tumors."

ZD1694 (tomudex)

"Specific TS inhibitor active in a range of malignancies"

"Single agent activity in phase 2 studies in colorectal, nscl, pancreatic, breast, and ovarian cancers"

"Activity seen in phase 2 chemoradiation studies of raltitrexed [tomudex] alone and in combination with oxaliplatin as preoperative therapy for rectal cancer"

"Activity seen in the first and second-line therapy of advanced colorectal cancer in combination with oxaliplatin"

"Manageable toxicity profile"

ZD0473

"There was evidence of antitumor activity in ovarian cancer patients"

"ZD0473 has a predictable and manageable toxicity profile"

ZD9238 (faslodex)

"In conclusion, FAS [faslodex] was at least as effective as ADX [Arimidex], with a non-significant numerical increase OR observed."

Section 21 CFR 312.7 states, among other things, that an investigational new drug may not be promoted as being safe or effective for uses under investigation. Therefore, the above claims are in violation of the Act.

Requested Action

AstraZeneca should immediately cease the distribution of these and other similar promotional materials for the above drugs that contain the same or similar claims or presentations. AstraZeneca should submit a written response to DDMAC on or before July 23, 2001, describing its intent and plans to comply with the above. In its letter to DDMAC, AstraZeneca should include the date on which this and other similarly violative materials were discontinued.

AstraZeneca should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID # 10135 in addition to the NDA number. DDMAC reminds AstraZeneca that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Grillo
7/9/01 08:43:18 AM

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Proceedings of ASCO Volume 20 2001

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The Combined Use of Goserelin and Anastrozole as Second Line Endocrine Therapy in Premenopausal Women with Advanced Breast Cancer - a Study of its Clinical and Endocrine Effects. *K. Cheung, D. Forward, L. Jackson, J. Robertson; Professorial Unit of Surgery, Nottingham City Hospital, Nottingham, UK*

Fifteen premenopausal women with either metastatic (N = 12) or locally advanced primary breast cancer (N = 3) were treated with a combination of a gonadotropin releasing hormone (GnRH) agonist, goserelin, (Zoladex (Z)) and a third-generation selective aromatase inhibitor, anastrozole (Arimidex (A)). All had previously been treated with Z and tamoxifen (T). Clinical Effects: Eleven women (73%) achieved objective response/durable stable disease (OR/SD) at 6 months with a median duration of remission of 16+ months (range: 6 - 41 months). Two remain in OR/SD but have yet to achieve 6 months of therapy. Two progressed before 6 months. Endocrine Effects: The introduction of Z+T resulted in an 89% reduction in serum estradiol (E2) levels compared to pre-treatment ($p < 0.05$). Substitution of T by A on progression resulted in a further 76% fall ($p < 0.05$) associated with clinical regression %. FSH levels were initially suppressed with Z+T

	Pre-Z+T	6 months on Z+T	3 months on Z+A	6 months on Z+A
Mean E2 (pmol/L)	224	24	6	5

falling from pre-Z+T levels of 10 IU/L (mean) to 1.6 IU/L ($p < 0.05$). Substitution of T by A led to a partial loss of this suppression with levels rising towards pre-treatment values (5.4 IU/L). LH levels were suppressed as would be expected by constant administration of a GnRH agonist. A non-significant fall from 0.34 to 0.20 pmol/L was seen when T was substituted by A. Testosterone, DHES and androstenedione, precursors in the estrogen synthesis pathway, showed small falls during the course of treatment. This study shows that Z+A induces therapeutic remission in a reasonable proportion of premenopausal women with advanced breast cancer who have progressed on Z+T. The clinical therapeutic effects are associated with demonstrable endocrine changes including a dramatic reduction of E2 levels seen in postmenopausal women receiving A alone.

ZD1839 ('Iressa')

MEDICAL INFORMATION PACK

For Medical Information Only -
Not Approved in US

AstraZeneca
ONCOLOGY

ORAL ADMINISTRATION OF THE SELECTIVE EGFR TYROSINE KINASE INHIBITOR, ZD1839 ('IRESSA'), IS ACTIVE AGAINST EGFR-OVEREXPRESSING INTRACRANIAL TUMORS

AB Heimberger, GE Archer, RE McLendon, D Price, AH Freidman, DB Bigner, JH Sampson

Duke University Medical Center, Durham, NC27710, USA

380

INTRODUCTION

- ZD1839 ('Iressa') is an orally active, selective EGFR-TKI (epidermal growth factor receptor-tyrosine kinase inhibitor) which blocks signal transduction pathways implicated in proliferation and survival of cancer cells, and other host-dependent processes promoting cancer growth.
- In animal studies, ZD1839 has been shown to be well tolerated and has demonstrated notable antitumor activity in a broad range of established human tumor xenografts [1]
- ZD1839 has been shown to have promising clinical efficacy, particularly in NSCLC, and to be well tolerated in Phase I studies.[2,3]
- The purpose of this study was to examine the *in vivo* efficacy of ZD1839 against intracranial tumors sequestered by the blood-brain barrier (BBB).

METHODS

In vitro growth inhibition assays

- Growth inhibition was assessed using 5×10^4 A431 or NR6M cells at logarithmic growth, treated with a final concentration of 0, 0.5, 1, 5, 10 or 20 µM ZD1839.

In vivo growth inhibition assays

- Xenografts utilized were A431 (which over-expresses the wild-type EGFR), and NR6M (which expresses the mutant EGFRvIII lacking a ligand binding domain, but containing a constitutively activated tyrosine kinase).

Subcutaneous tumors

- These were initiated by implantation of 1×10^6 A431 cells suspended in 100 µL saline, into the right flank of nude mice.
- Mice were treated daily, starting 10 days after tumor implantation (when the tumors achieve a palpable volume of 0.4 cm^3), with ZD1839 at 100 mg/kg/day for a total of 13 days or a vehicle control at which time control tumors became necrotic. All treatments were administered once daily by oral gavage.

Intracranial tumors

- Cells were resuspended in 2.5% methylcellulose and the lethal tumorigenic dose of 1×10^5 A431 cells were injected intracranially into nude mice.
- Treatment began 3 days after implantation (when tumors were histologically evident) and consisted of a total of 15 weekday doses, over 21 days, with ZD1839 (50 mg/kg/day or 100 mg/kg/day) or the vehicle control. All treatments were administered once daily by oral gavage.

Assessment of toxicity and efficacy in xenograft models

- Toxicity was monitored by daily weights, daily neurologic examinations, and post-mortem hematoxylin and eosin histologic examination of the brain and systemic organs in nude mice.
- Subcutaneous tumors were measured by volume. Survival of mice with intracranial tumors was monitored.

RESULTS

In vitro growth inhibition

- Dose-dependent growth inhibition was observed after incubation with ZD1839 in both A431 and NR6M cell lines. The IC_{50} values for A431 and NR6M cell lines were 3.2 µM and 5.6 µM, respectively (Figure 1).

In vivo growth inhibition

Subcutaneous tumor response

- ZD1839 markedly suppressed subcutaneous growth of A431 expressing the wild-type EGFR, although in no animal was there total elimination of the tumor (Figure 2).
- Upon withdrawal of ZD1839, all animals eventually had regrowth of subcutaneous tumors.
- No growth suppression was observed in mice with NR6M tumors.

Intracranial tumor response

- Treatment of mice with A431 tumors with ZD1839 at 50 mg/kg/day resulted in significantly greater median survival compared with mice receiving the vehicle control (34 vs 18 days; p=0.009).
- Treatment of mice with ZD1839 at 100 mg/kg/day resulted in significantly greater median survival compared with mice receiving the vehicle control (37 vs 18 days; p<0.001) (Figure 3).
- The median survival was significantly greater in the mice treated with ZD1839 100 mg/kg/day compared with those treated with 50 mg/kg/day (p=0.022).
- Treatment of mice with NR6M tumors with ZD1839 100 mg/kg/day resulted in a median survival of 10 days which was not statistically significantly (p=0.407) different from that of mice receiving the vehicle control (median survival 9 days).

Figure 1. ***In vitro*** **growth inhibition**

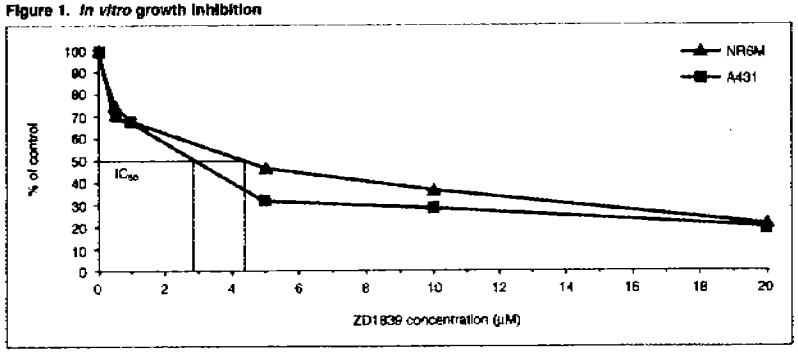


Figure 2. Oral administration of ZD1839 is efficacious against subcutaneous A431

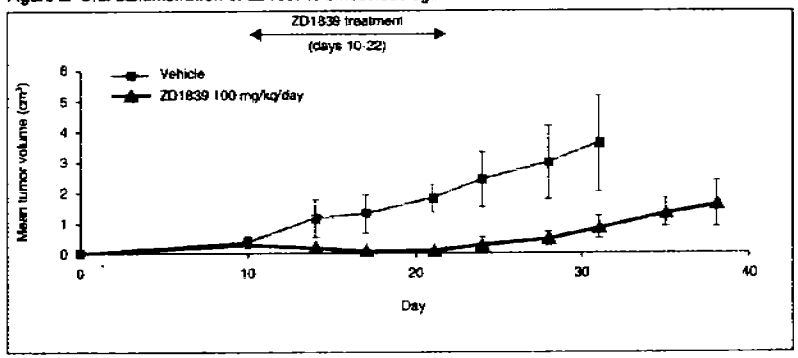
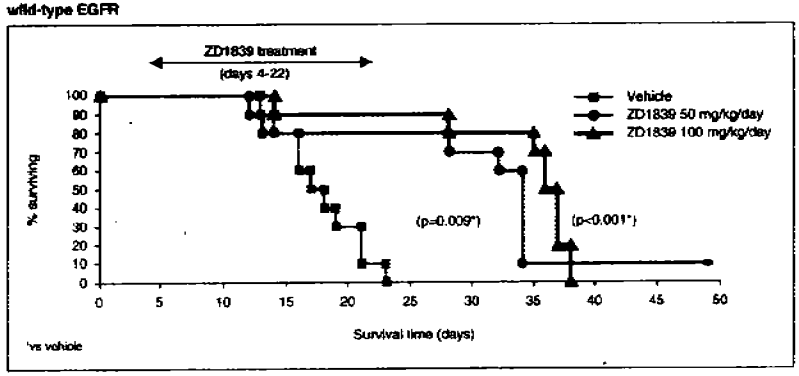


Figure 3. Oral administration of ZD1839 is efficacious against intracranial tumors expressing the wild-type EGFR



Toxicity in xenograft models

- No weight loss >10% nor any neurologic deficit was seen during the 28-day observation period for any treatment group. Histologic examination of the systemic organs and brain did not reveal any significant differences among nude mice treated with either dose of ZD1839 (50 mg/kg/day or 100 mg/kg/day) when compared with vehicle.

CONCLUSIONS

- ZD1839 inhibits the *in vitro* growth of both EGFR-expressing and mutant EGFRvIII-expressing cell lines.
- Orally administered ZD1839 is active against central nervous system tumors with limited or no systemic toxicity.
- This is highly significant since many of the systemic cancers such as breast and non-small lung carcinoma, both of which express or overexpress the EGFR, find refuge in the central nervous system due to limited penetration of the BBB by standard systemic chemotherapeutics.
- It is possible that intracranial implantation may disrupt the BBB, allowing ZD1839 to enter central nervous system lesions. However, malignant disease and metastases are often accompanied by marked disruption of the BBB, which may be sufficient to allow ZD1839, a small molecule, access to this privileged site.
- No systemic or neurologic toxicity was associated with treatment of nude mice with ZD1839.
- There are only a few orally administered chemotherapeutics currently available that have shown Phase III efficacy for the treatment of malignant gliomas, with their poor prognosis and universal over-expression of the EGFR and mutant EGFR.
- ZD1839 may have some potential as a new agent for the treatment of these tumors.

References

1 Woodburn, JR, et al Proc Am Assoc Cancer Res 1997; 38: A4251.

2 Kris M, et al Clin Cancer Res 1999; 5(Suppl): 3749S-3750S, abs 99

3 Baselga, J, et al Clin Cancer Res 1999; 5(Suppl): 3735S abs 29

'Iressa' is a trade mark of the AstraZeneca group of companies

POTENTIATION OF CYTOTOXIC DRUG ACTIVITY IN HUMAN CANCER CELLS BY ZD1839 ('IRESSA'), AN EGFR-SELECTIVE TYROSINE KINASE INHIBITOR

3075

F Ciardiello, R Caputo, R Bianco, V Damiano, G Pomatico, S De Placido, AR Bianco, G Tortora

Division of Medical Oncology, University of Naples Federico II, Naples, Italy

INTRODUCTION

- ZD1839 ('Iressa') is an orally active, selective EGFR-TKI (epidermal growth factor receptor tyrosine kinase inhibitor) which blocks signal transduction pathways implicated in cancer cell proliferation, survival and other host-dependent processes promoting cancer growth.
- In preclinical studies, ZD1839 has been shown to be well tolerated, and has shown antitumour activity in a broad range of established human tumour xenografts.
- ZD1839 has been shown to have promising clinical efficacy and to be well tolerated in intermittent and continuous dosing schedule Phase I/II studies.
- The aim of this study was to examine the antiproliferative and antitumour activity of ZD1839 treatment. In addition, since the antitumour activity of various cytotoxic drugs is potentiated using monoclonal antibodies that block the EGFR, the antitumour activity of ZD1839 in combination with other cytotoxic drugs was evaluated.

METHODS

Growth inhibition and apoptosis in vitro

- Four cell lines were used: GEO (colon), OVCAR-3 (ovarian), ZR-75-1 (breast) and MCF-10A Ha-ras (MCF-10A breast cells co-transfected with c-Ha-ras proto-oncogene).
- Growth inhibition was assessed using a standard soft agar colony forming assay. 10^4 cells were treated with different concentrations of ZD1839 alone (0.01–25 µM daily, from days 2 to 5) or in combination with a cytotoxic agent. Colonies were counted after 10 to 14 days.
- Apoptosis was determined in 6-well plates (Nunc) (duplicate) 4 days after treatment with ZD1839 alone (0, 0.05, 0.1, 1.0 µM each day for 3 days) or in combination with a cytotoxic agent using the Cell Death Detection ELISA Plus Kit (Boehringer Mannheim), which measures DNA fragments in the supernatants of lysed cells.
- Cytotoxic agents used were: cisplatin, carboplatin, docetaxel, etoposide, paclitaxel, topotecan, doxorubicin, oxaliplatin and raltitrexed ('Tomudex'). These were added on day 1 (cisplatin, carboplatin, docetaxel, etoposide, paclitaxel, doxorubicin and oxaliplatin) or on days 1 and 2 (topotecan and raltitrexed).

Growth inhibition in vivo using established GEO tumour xenografts

- Nude mice bearing GEO tumour xenografts were dosed with ZD1839 (1.25–5 mg/mouse/day) intraperitoneally (ip) on days 1 to 5 of each week, for 4 weeks, commencing 1 week after inoculation of the xenograft.
- In combination studies, mice were dosed with ZD1839 (2.5 mg/mouse/day, ip on days 1 to 5 of each week, for 4 weeks) and a variety of cytotoxic agents at their maximum tolerated doses (paclitaxel 20 mg/kg, topotecan 2 mg/kg or raltitrexed 12.5 mg/kg) on day 1 of each week, for 4 weeks.
- Ten mice per study group were included.
- Mice were humanely sacrificed when tumours reached approximately 2 cm.

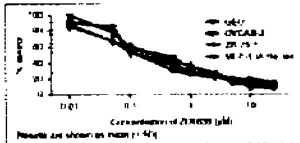
RESULTS

Growth inhibition and apoptosis in vitro

ZD1839 treatment

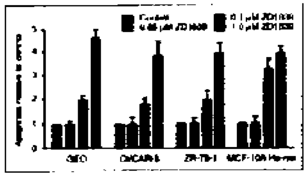
- ZD1839 treatment produced a dose-dependent growth inhibition in all human cancer cell lines tested (Figure 1).
- An increase in apoptotic cell death (2- to 4-fold) was observed at higher doses of ZD1839 (>0.1 µM) in all cell lines (Figure 2).

Figure 1. Dose-dependent growth inhibitory effects of ZD1839 on GEO, OVCAR-3, ZR-75-1 and MCF-10A Ha-ras cell lines using soft agar colony forming assay



Results are shown as mean (n=4)

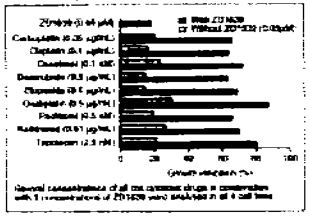
Figure 2. Induction of apoptosis in GEO, OVCAR-3, ZR-75-1 and MCF-10A Ha-ras cell lines



ZD1839 combination treatment

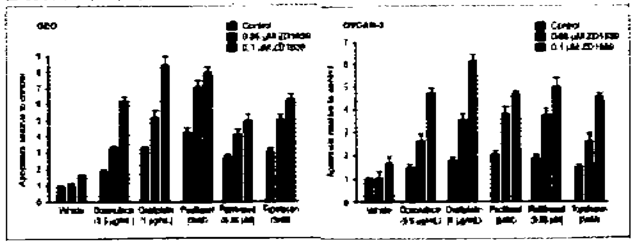
- Growth inhibition in all cell lines was potentiated by exposure to ZD1839 in combination with a range of cytotoxic drugs (Figure 3).
- Apoptosis was enhanced in GEO and OVCAR-3 cells by administration of ZD1839 in combination with paclitaxel, topotecan, doxorubicin, oxaliplatin and raltitrexed compared with ZD1839 treatment alone (Figure 4).

Figure 3. Growth inhibitory effects of ZD1839 in combination with cisplatin, carboplatin, docetaxel, etoposide, paclitaxel, topotecan, doxorubicin, oxaliplatin, and raltitrexed in the GEO cell line



Several concentrations of all the cytotoxic drugs in combination with 3 concentrations of ZD1839 were analysed in all 4 cell lines

Figure 4. Induction of apoptosis by ZD1839 alone or in combination with paclitaxel, topotecan, doxorubicin, oxaliplatin, and raltitrexed in the GEO (upper panel) and OVCAR-3 (lower panel) cell lines

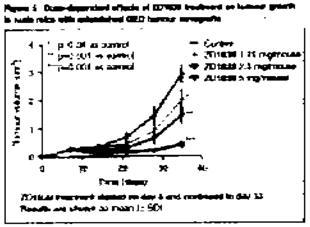


Growth inhibition in vivo using established GEO tumour xenografts

ZD1839 treatment

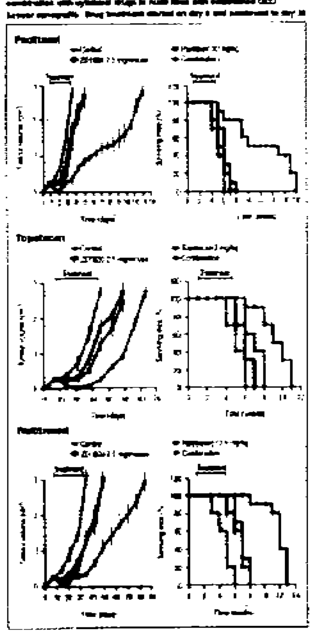
- Administration of ZD1839 was associated with dose-dependent antitumour activity in mice with established GEO tumour xenografts in vivo (Figure 5).
- Survival in mice with established GEO tumour xenografts was increased by administration of ZD1839.

Figure 5. Dose-dependent effects of ZD1839 treatment on tumour growth in nude mice with established GEO tumour xenografts



ZD1839 treatment started on day 8 and continued to day 33. Results are shown as mean (±SD)

Figure 6. Antitumour activity and survival benefits of ZD1839 treatment in combination with cytotoxic drugs in nude mice with established GEO tumour xenografts. Drug treatment started on day 8 and continued to day 35



ZD1839 combination treatment

- A significant increase in growth inhibition was observed in mice with established GEO tumour xenografts when treated with ZD1839 in combination with paclitaxel, topotecan or raltitrexed compared with ZD1839 (p<0.01) or cytotoxic drug treatment alone (p<0.01) (Figure 6).
- ZD1839 combination treatment with paclitaxel, topotecan or raltitrexed was accompanied by a significant increase in survival compared with ZD1839 (p<0.001, p<0.02, p<0.01, respectively) or with cytotoxic drug treatment alone (p=0.001, p=0.05, p<0.01, respectively) (Figure 6).
- ZD1839 combination treatment was well tolerated in vivo.

CONCLUSIONS

References

1. Woodburn JR, et al. Proc Am Assoc Cancer Res 1997; 38: 4251.
2. Arteaga, et al. Clin Cancer Res 1999; 5(suppl): 3778s-3779s.
3. Baselga J, et al. Clin Cancer Res 1999; 5(suppl): 3765s.
4. Ciardiello F, et al. Clin Cancer Res 1999; 5: 909-916.

'Iressa' and 'Tomudex' are trade marks, the property of the AstraZeneca group of companies

AACR, SAN FRANCISCO, CA, APRIL 1–5, 2000

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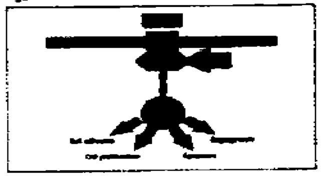
M Kris,[1] M Ranson,[2] D Ferry,[3] L Hammond,[4] S Averbuch,[5] J Ochs,[5] E Rowinsky[4]

[1]Memorial Sloan-Kettering Cancer Center, New York, USA; [2]Christie Hospital, Manchester, UK; [3]Queen Elizabeth Hospital, Birmingham, UK; [4]Cancer Therapy and Research Center, San Antonio, USA; [5]AstraZeneca, Wilmington, USA

Background

- ZD1839 ('Iressa') is an orally active, selective EGFR-TKI (epidermal growth factor receptor tyrosine kinase inhibitor) which blocks signal transduction pathways implicated in cancer cell proliferation, survival and other host-dependent processes promoting cancer growth (Figure 1)

Figure 1. Mechanism of action of ZD1839



- Significant growth delay has been observed following ZD1839 oral dosing in a range of human tumor xenografts, and tumor regression has been observed at a high dose (200 mg/kg/day)
- Clinical trials in healthy volunteers support the use of ZD1839 as a daily oral treatment

Objectives

- Primary: to evaluate the tolerability and toxicity of escalating daily oral doses of ZD1839 for 14 days, in patients with solid malignant tumors known to overexpress EGFR
- Secondary: to examine the pharmacokinetics and antitumor activity of ZD1839

Study design

- Open, Phase I, rising multiple-dose, sequential dose escalation trial

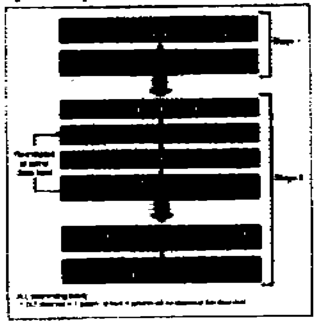
Patients

- Aged ≥18 years and expected to survive for >12 weeks
- Solid, malignant tumors of types known to overexpress EGFR, refractory to other treatments or for which there is no standard therapy
- WHO performance status of ≤2

Treatment

- Once-daily oral administration of ZD1839 in an intermittent schedule (Figure 2)

Figure 2. Dosing schedule for ZD1839



Tolerability

- Dose-limiting toxicity (DLT) was defined as any drug-related toxicity ≥ common toxicity criteria (CTC) grade 3 or 4, significant corneal epithelial change or PR interval prolongation in ≥2 patients at a particular dose level

Antitumor activity

- Tumor assessments were made by bidimensional imaging
- Objective response criteria were based on UICC/WHO criteria

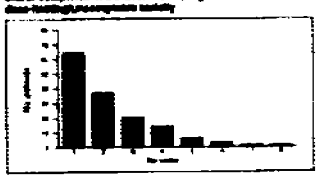
Patients

- 64 patients (35 male; 29 female) with a median age of 61 years (range 28–78) and median WHO performance status (PS) of 1 (18=PS0; 41=PS1; 5=PS2) were enrolled in the trial
- Tumor types and dose levels are shown in Table 1
- 148 treatment cycles (range 1–8) of 28 days were begun and/or completed in the absence of progressive disease (Figure 3)

Table 1. Dose levels by tumor types

[illegible]

Figure 3. Total number of 28-day treatment periods begun and/or completed in the absence of progressive disease or dose-limiting/unacceptable toxicity



Tolerability

- DLT was reached at the 700 mg dose level, with grade 3 diarrhea in 2 patients (Table 2)

Table 2. Selected mechanism-based adverse events by patient according to CTC grade and dose of ZD1839 in cycles 1 and 2

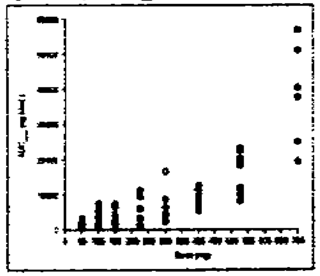
[illegible]

- Three patients were withdrawn from the study due to drug-related toxicity: 1 patient with a pruritic grade 3 skin rash at the 525 mg dose level and 2 patients with grade 3 diarrhea at the 700 mg dose level. All drug-related adverse effects resolved following discontinuation of treatment
- The most frequently reported organ system adverse events of any etiology were gastrointestinal and skin; non-specific symptoms were common
- Grade 3/4 adverse events were rare and usually – directly or indirectly – related to disease progression (Table 2)

Pharmacokinetics

- The mean C_{max} and AUC_{0-24} at 50 to 700 mg/day after 14 days ranged from 113 to 2266 ng/mL and from 1823 to 38483 ng.h/mL, respectively (Figure 4). The mean elimination half-life was 48 hours, which is compatible with once-daily dosing

Figure 4. Steady-state AUC_{0-24} versus ZD1839 dose



Antitumor activity

- Fourteen patients with a range of tumor types had stable disease or responses for at least 4 months. One patient had significant regression of evaluable disease, non-bulky disease on chest x-ray, but relapsed in the brain prior to the 3rd cycle (Table 3)
- Significant antitumor response was most evident amongst the 16 previously treated NSCLC patients
- Two patients with NSCLC receiving 225 mg and 400 mg of ZD1839 had a partial response. These patients continue to show a partial response (8+ and 6+ months, respectively) (Table 3; Figure 5)

Figure 5. CT scan of patient with NSCLC, pre-treatment and after 3 and 5 months' treatment with ZD1839 [illegible]

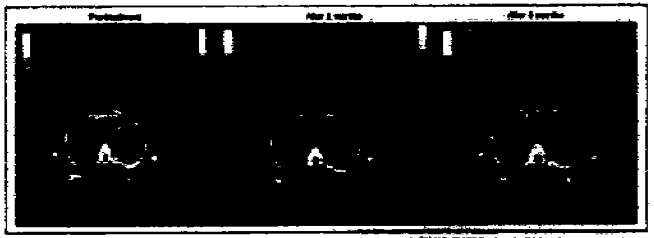
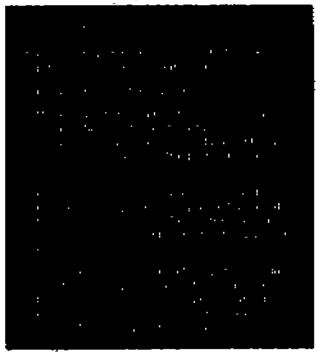


Table 3. Patients on ZD1839 therapy with radiographic response or significant regression of any duration or stable disease ≥4 months

[illegible]

- Two patients had confirmed significant regression of non-measurable, evaluable disease (Table 3)
- Currently 7 patients, including 4 NSCLC patients and 1 colorectal, ovarian and [illegible] cancer patient are continuing ZD1839 treatment in this trial (4–8+ months)



References

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ONCOLOGY

PHASE I AND PHARMACOKINETIC STUDY OF CIS-AMMINEDICHLORO(2-METHYLPYRIDINE) PLATINUM(II) (ZD0473), A NOVEL STERICALLY HINDERED PLATINUM COMPLEX, IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES

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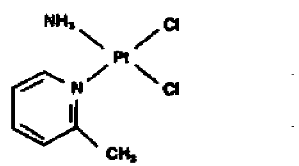
- There is a significant clinical need to develop new platinum anticancer agents that overcome intrinsic or acquired mechanisms of resistance, and have toxicity profiles at least no worse than currently available agents.
- ZD0473 is a novel, sterically hindered platinum II complex, synthesised to overcome acquired platinum resistance due to glutathione detoxification (Figure 1).[1]

Figure 1. ZD0473



- The ability of ZD0473 to overcome acquired resistance to cisplatin in vitro and in human tumor xenografts has been demonstrated.[1]
- The dose-limiting toxicity (DLT) in animals was myelosuppression in the absence of nephro- or neurotoxicity.[2]
- The toxicity and pharmacokinetics of ZD0473 were examined in this Phase I trial involving patients with advanced solid malignancies.

Study design and selection criteria

- A dose-escalating, pharmacokinetic trial.
- Patients had advanced solid malignancies.
- The patient demographics and tumor types are shown in Table 1.
- The trial commenced in November 1997 at the Royal Marsden Hospital, UK.

Table 1. Patient demographics and tumor types

No. patients enrolled	27
Male/female	11/16
Median age (range), years	54 (33–71)
Total no. cycles	81
Performance status	
0	11
1	14
2	2
Prior treatment (regimens)	
≤ 1	10
>1	17
Tumor types	
Ovary	4
Non-small cell lung	3
Mesothelioma	4
Head and neck	1
Colorectal	2
Breast	2
Melanoma	1
Cervix	1
Kidney	2
Unknown primary	2

Treatment

- Pharmacokinetic-guided dose escalation was employed (Table 2). The starting dose was 12 mg/m² (1/10 LD10 in mice).

Table 2. Dose and dose sequence summary

Dose level (mg/m²)	No. patients	No. cycles per patient
12	3	4, 5, 2
24	3	2, 5, 3
48	3	2, 5, 2
96	3	4, 2, 6
130	5	1, 6, 2, 1, 2
110	6	6, 2, 4, 6, 1
120	3	2, 1, 1
150	2	6, 2

- ZD0473 was administered intravenously by infusions of duration of 1 h (final volume up to 200 mL) or 2 h (larger volumes).
- ZD0473 was administered to patients every 3 weeks at dose levels 12 to 96 mg/m². At doses higher than 96 mg/m² most patients received the drug every 4 weeks.

Pharmacokinetics

- The pharmacokinetic profile of ZD0473 was analysed using a 3-compartmental model with no weighting.
- Platinum was measured by atomic absorption spectrophotometry.

Assessments

- Toxicity (CTC grade) was assessed by adverse events. DLT (first cycle) was defined as: ≥ patients with:
  - grade 3/4 thrombocytopenia;
  - grade 4 neutropenia >5 days;
  - neutropenic fever;
  - grade 3/4 nonhematological toxicity.
- Objective response was recorded as complete response, partial response, stable disease or disease progression.

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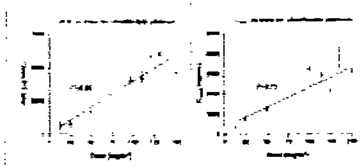
Pharmacokinetics

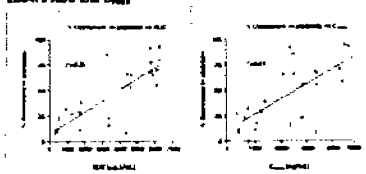
- AUC and C_{max} increased linearly with increases in dose (r^2 = 0.88 and 0.73, respectively; Figure 2).

Figure 2. ZD0473 AUC and C_{max} as a function of dose



- The percentage decrement of platelets as a function of AUC and C_{max} is given in Figure 3. Plasma AUC correlated with thrombocytopenia (r^2 = 0.81).

Figure 3. Percentage decrement in platelets as a function of ZD0473 AUC and C_{max}



- The elimination was triphasic, with mean α, β, and γ half lives of 0.2, 2.0 and 78 h, respectively (Table 3).

Table 3. Mean (SD) ZD0473 pharmacokinetics (plasma ultrafiltrate)

Dose (mg/m²)	CL (L/h)	V_{ss} (L)	$t_{1/2}α$ (h)	$t_{1/2}β$ (h)	$t_{1/2}γ$ (h)
12	10 (2)		0.2 (0.1)	1.4 (0.6)	-
24	10 (2)		0.1	1.5 (0.1)	-
48	21 (3)	–	0.3 (0.2)	2.4 (0.6)	
96	45 (58)	1125 (680)	0.2 (0.1)	1.8 (1.7)	86 (100)
110	13 (4)	464 (314)	0.2 (0.1)	1.4 (0.3)	52 (44)
130	6 (4)	547 (467)	0.3 (0.3)	1.7 (0.6)	93 (45)
120	9 (1)	335 (232)	0.4 (0.3)	3.7 (4.5)	81 (27)
150	15	391	0.04	1.2	178
Overall	14 (30)	582 (548)	0.2 (0.2)	2.0 (2.2)	78 (56)

- Overall, excretion of ZD0473 in the urine over 24 h ranged from 5 to 70% of the dose, ranging from 20 to 30% in the majority (90%) of patients.

Toxicity profile

- At a dose level of 96 mg/m², ultrafiltrate platinum AUC was 70% of the AUC observed in the mouse at the maximum tolerated dose (MTD).
- The number of patients experiencing toxicity at each dose level and the grade of the toxicity are given in Table 4.

Table 4. Toxicity at each dose level in all cycles

	No. patients (grade*)								CTC Grade			
Toxicity	12	24	48	96	110	120	130	150	1	2	3	4
Hematological												
Anemia	-	-	-	1 (2)	4 (2)	1 (2)	1 (2)	2 (2)	5	1	2	-
Leucopenia	-	-	1 (1)	1 (2)	1 (3)	1 (1)	2 (2)	1 (2)	2	6	5	-
Neutropenia	-	-	-	1 (2)	2 (2)	1 (1)	2 (2)	2 (2)	5	2	-	-
Thrombocytopenia	-	-	1 (1)	1 (3)	1 (3)	2 (1)	3 (4)	1 (4)	5	2	3	3
Nonhematological												
Nausea	-	1 (2)	1 (1)	1 (2)	1 (2)	1 (2)	3 (2)	1 (2)	5	6	3	
Vomiting	-	1 (2)	2 (1)	1 (2)	1 (2)	-	1 (2)	1 (1)	6	3	2	-
Fatigue	-	-		1 (1)	2 (2)	2 (2)		2 (1)	4	4		-
Taste disturbance	-	1 (1)	-	1 (1)	-	1 (1)	-	-	3	-	-	-
Peripheral neuropathy					-	-	-	1 (1)	1	-	-	-

* The highest grade of toxicity for any patient is given.

- When the dose was increased to 130 mg/m², DLT was observed (3 of the 5 patients with poor performance status [PS] had grade 3/4 thrombocytopenia and 2 patients had grade 3 neutropenia).
- The 130 mg/m² dose was de-escalated to 110 mg/m² and treatment was given every 4 weeks, as most patients were unable to receive doses every 3 weeks at the higher dose level.
- At 110 mg/m², no patient experienced grade 3 or 4 hematologic toxicity. The dose was then increased to 120 and 150 mg/m² every 4 weeks, and only patients with good PS were included.
- At 120 mg/m², no patient experienced DLT, whereas at 150 mg/m² 1 patient experienced DLT of grade 4 thrombocytopenia.

Response

- The number of patients evaluated for response was 22.
- A partial response, with a >50% fall in CA125, has been observed in 1 patient with recurrent ovarian carcinoma (previously sensitive to carboplatin and paclitaxel) after 1 cycle of ZD0473 at 150 mg/m².
- Four patients have had prolonged stable disease:
  - One patient with ovarian carcinoma resistant to cisplatin, carboplatin and topotecan had a >50% fall in CA125, and stable disease after 6 cycles of ZD0473 at 96 mg/m²
  - One patient with squamous laryngeal carcinoma sensitive to cisplatin who had received ZD0473 at 130 mg/m²
  - Two patients who had received ZD0473 at 110 mg/m², one with nasopharyngeal carcinoma resistant to carboplatin and one patient with non-small cell lung cancer refractory to cisplatin.

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References

1. [illegible]
2. [illegible] Clinical Cancer Research [illegible]

Howell A, Robertson JFR, Albano J Quaresma, et al . COMPARISON OF EFFICACY AND TOLERABILITY OF FASLODEX™ (ICI 182,780) WITH ARIMIDEX™ (ANASTROZOLE) IN POST-MENOPAUSAL (PM) WOMEN WITH ADVANCED BREAST CANCER (ABC) - PRELIMINARY RESULTS.

Abstract Presented at: San Antonio Breast Cancer Symposium, December 2000

COMPARISON OF EFFICACY AND TOLERABILITY OF FASLODEX™ (ICI 182,780) WITH ARIMIDEX™ (ANASTROZOLE) IN POST-MENOPAUSAL (PM) WOMEN WITH ADVANCED BREAST CANCER (ABC) - PRELIMINARY RESULTS.

[1]A Howell, [2]JFR Robertson, [3]J Quaresma Albano, [4]A Aschermannova, [5]L Mauriac, [6]U Kleeberg, [7]I Vergote, [8]B Erikstein, [9]A Webster, [9]C Morris. [1]Christie Hospital, UK; [2]Nottingham, UK; [3]Coimbra, Portugal; [4]Nova Ves Plod Plesi, Czech Republic; [5]Bordeaux, France; [6]Hamburg, Germany; [7]Leuven, Belguim; [8]Oslo, Norway; [9]AstraZeneca UK.

'Faslodex' (ICI 182,780) (FAS) is a novel, estrogen receptor downregulator. We report here on a phase III clinical trial [0020], which compared FAS 250mg intramuscular (i.m.) injection once monthly and 'Arimidex' (anastrozole) (ADX) 1mg od in PM women with ABC who had progressed or recurred on prior endocrine treatment for early or advanced breast cancer.

An open, randomized, multi-center, parallel-group, trial was conducted to compare the efficacy and tolerability of FAS with ADX. The primary endpoint was time to progression (TTP). Secondary endpoints included objective response (OR) rates, duration of response (DOR) and tolerability. Patients were randomised to either FAS 250mg (1 x 5ml) (n=222) i.m. once monthly or ADX 1mg (n=229) orally od. Patients were recruited between June 1997 and September 1999 and followed for a median of 305 days. At the time of analysis approximately 83% of patients in each treatment arm had progressed. Median TTP was 167 days and 156 days for FAS and ADX respectively (Hazard ratio 0.97; Confidence Limits 0.79,1.28; p = 0.78). Objective response (OR, CR+PR) rates showed a non-significant numerical advantage for FAS over ADX, OR rates being 20.7% and 15.7% for FAS and ADX respectively (Odds ratio 1.38; Confidence Limits 0.84,2.29; p= 0.20),with the odds of attaining OR being 38% higher for FAS treated patients. Clinical benefit rates (CR+PR+SD≥24 weeks) were 44.5% and 45.0% for FAS and ADX respectively. Median duration of response was 434 days for FAS and 425 days for ADX.

Both treatments were well tolerated with 3.2% of FAS patients and 2.2% of ADX patients withdrawn due to adverse events. For FAS and ADX, side effects included: hot flushes, 18.6% and 17%; gastrointestinal disturbances, 40.0% and 34.3%; weight gain 0.5% and 1.7%; vaginitis 0.5% and 0.9%.

In conclusion, FAS was at least as effective as ADX, with a non-significant numerical increase in OR observed.